The Story of NAIMIT – A Framework 7 Project on Type 1 Diabetes

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Abstract

NAIMIT (acronym for Natural Immune Modulation for Intervention in Type 1 Diabetes) is a large-scale collaborative programme of the 7th framework from the European Commission. The aim of the consortium is to bring together a group of leading European researchers spanning the field from genetics, through pancreatic beta-cell, dendritic cells and T-cell biology, towards clinical interventions. The ultimate goal is to develop novel and personalised interventional therapies in recent-onset type 1 diabetic patients, with minimal immune system interference, leading to beta-cell protection and restoration, based on a solid understanding of the disease pathogenesis, enabling experimental findings to be adopted for clinical applications.

Keywords

Type 1 diabetes, intervention, personalised therapies

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Type 1 diabetes (T1D) is a relatively rare disease, but attracts much attention as it is a lifelong disease that mainly starts during childhood, thus condemning children to the daily administration of subcutaneous insulin injections, accompanied with a need for painful finger sticks in order to measure glucose levels and an often restrictive lifestyle. Patient advocacy groups, like the Juvenile Diabetes Research Foundation (JDRF), have succeeded in putting T1D on the map and attracting research funds. Research in the T1D field has been intense, with growing insights in the pathogenesis of the disease, but the true aetiology of, and, more importantly, effective and safe interventions to prevent or arrest, let alone cure, the disease remain elusive.

In one of the final calls in the ambitious European Commission's Framework 7 programme (EC FP7), projects focusing on better understanding of the disease and testing interventions to arrest the disease, taking into account both the immune system and the beta-cell, were sought. Natural Immune Modulation for Intervention in Type 1 diabetes (acronym NAIMIT), is the official title of this 5-year project that was funded by the EC and that is running in its final year. Here we share some of the elements of why we believe this project is considered successful.

1. The right team with ambitious small and medium-sized enterprise (SME) partners.
2. An open and logical concept.
3. Realistic objectives and aims.
4. Clear guidelines and support of the EC via scientific officers.
5. Communication, communication, communication.

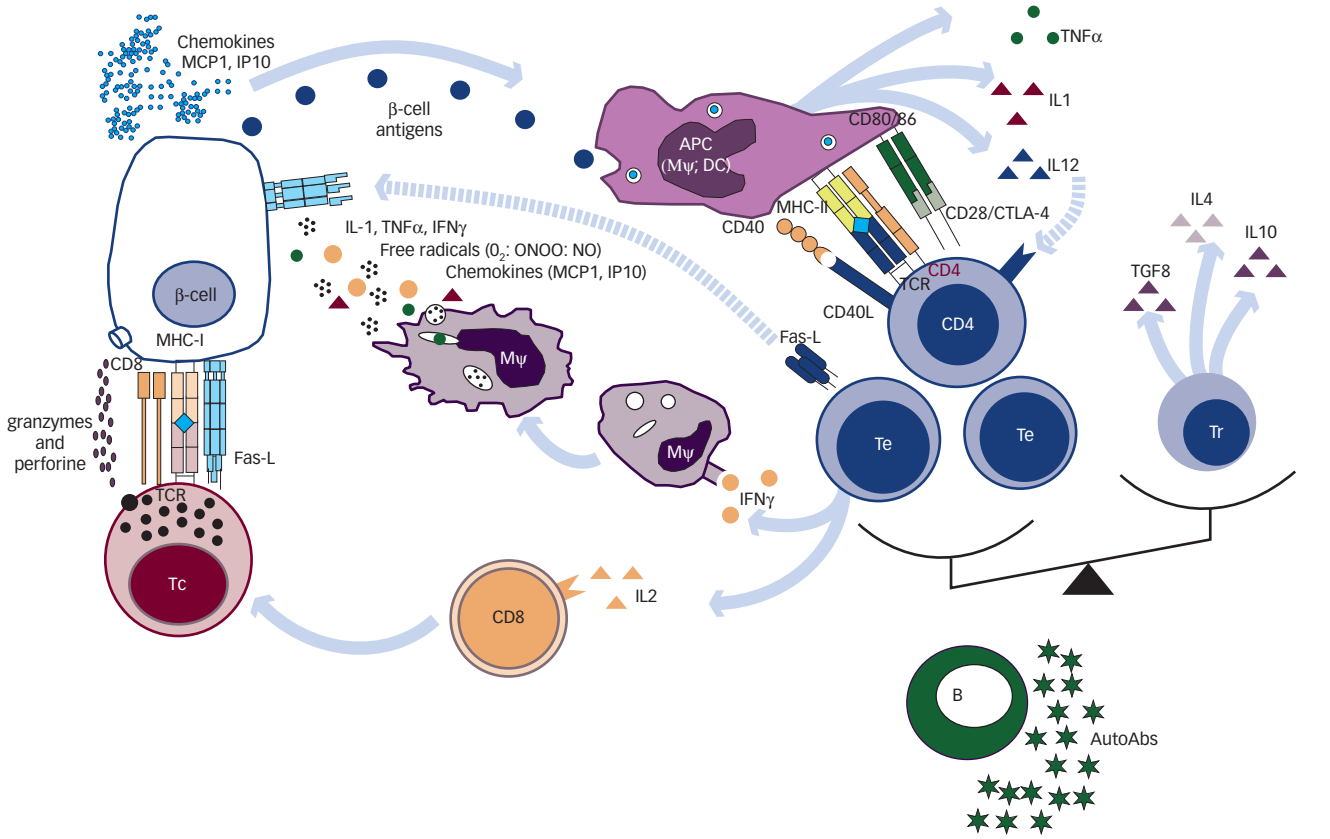
The NAIMIT Team

In response to the EC FP7 call, we have put together not a 'diplomatic' or 'strategic' consortium, but a consortium of researchers from different disciplines, most of whom having already closely collaborated with each other in the past and all of whom were high-level scientists with a profile that was optimal for the realisation of the goals of the call. A nucleus of five to six 'leaders' came together and led all the brainstorming sessions, the writing and the task distribution, with assignment of strong profiles as work package (WP) leaders. Importantly, SMEs with whom some of the partners had collaborated in the past and that had technologies or tools ready for use and leverage were approached successfully. These SMEs were small, but ambitious, and at a point in their development where a FP7 project could mean a turning point. One SME, ImmunoCore, has since entered into a major venture, whereas another realised that T1D was not their main interest after all and left the consortium. This transition was painless, thanks to the excellent guidance of the scientific officer at the EC and a clear consortium agreement. The deliverables that depended on the SME that left the consortium were taken over by another partner, thus avoiding any interference with the master plan behind NAIMIT.

The NAIMIT Concept

The goals of a successful therapeutic approach to T1D are cessation of beta-cell destruction, reversal of autoimmunity and preservation of surviving beta-cells, allowing any natural regenerative potential to be realised. These are crucial challenges for diabetes research. Any such

Figure 1: A Proposed Model for the Pathogenesis of Type 1 Diabetes



Viral infections or other triggers can initiate a hyperactive response towards the beta-cells, releasing beta-cell antigens and possibly also chemokines that may contribute to the homing and activation of T lymphocytes and antigen-presenting cells (APCs) into the islets. The beta-cell antigens are presented in association with class II major histocompatibility complex (MHC) molecules to CD4+ T lymphocytes after being processed by the dendritic cells (DCs). DCs release interleukin (IL)-12, activating CD4+ T effector (Te) cells, which in turn release interferon (IFN)-γ and IL-2. Migratory macrophages and CD8+ T lymphocytes become cytotoxic (Tc) in response to these cytokines and release IL-1ß, tumour necrosis factor alpha (TNF-α), IFN-γ, free radicals and chemokines. CD8+ Tc cells recognise beta-cell antigens in association with class I MHC molecules. Beta-cells can also be destroyed by Fas-mediated cell death and/or granzyme and perforin. Regulatory T cells (Tregs) are dysfunctional or not sufficiently present. IP-10 = interferon-gamma-inducible protein-10; MCP1 = monocyte chemoattractant protein 1; TGFβ = transforming growth factor beta. GMP = good manufacturing practices; ISIS-Treg = islet-specific interleukin-10 secreting regulatory T cells; KO = knock-out; mTCRs = monoclonal T cell receptors; PIT = peptide immunotherapy; siRNA = silencing RNA.

interventions to achieve beta-cell protection and restoration should realise these goals through modulation of the immune system of the patient to a minimal degree in order to avoid severe disturbances of immune surveillance mechanisms leading to intolerable side effects. The present state of our understanding of the pathogenesis of T1D indicates that, in principle, therapeutic success is achievable and that interference in the progressive loss of beta-cell mass in newly diagnosed T1D patients is within reach. This requires innovative approaches that operate with a minimal degree of interference in the general functions of the immune system. In order to move the field forward in this respect, we have proposed a series of studies that represent a novel and integrated approach.

The underlying concept for the therapeutic interventions to be developed in this proposal was the central role of the immune system in T1D, but we also recognised the important role that the beta-cell adopts, as a partner actively contributing to its own demise (see *Figure 1*). This should undoubtedly be taken into account when designing strategies for therapeutic interventions for beta-cell protection and restoration. The concept of a key role for both the immune system and the beta-cell highlights the need for a 'multiple hit' approach to disease prevention. This approach should include both modulation and re-education of the immune system, boosting of beta-cell defenses against autoimmune damage and arresting the pro-inflammatory dialogue between immune cells and beta-cells.

The NAIMIT Objectives

The NAIMIT project followed from the concept proposed: if the interplay between the beta-cell and the immune system are central to the pathogenesis of the disease, both partners must be studied. Moreover, different parts of the immune system may be studied at the same time and if we want to interfere in a disease like T1D, where a treatment (although not perfect and cumbersome) exists, namely insulin therapy, we will only accept interventions that are soft and virtually without side effects. Finally, the use of steroids like VitD as immune modulators opens the road to personalised medicine, on the basis of genetic markers. Of interest, we decided to put 'the building of a consortium' by itself as one of the objectives, and in hindsight this is probably one of the most important objectives: to bring together a group of experts around one theme, thus creating synergy in methods and in ideas. Thus, the specific objectives were defined as:

1. To explore novel immunomodulatory approaches using natural immunomodulators (e.g. antigen, glucocorticoids [GCs] and vitamin D [VitD] derivatives) to modulate dendritic cell (DC) and T-lymphocyte function, both *in vitro* and *in vivo* with the aim of inducing antigen-specific regulation.
2. To introduce novel immunomodulatory tools to induce antigen-specific tolerance: monoclonal T cell receptors (mTCRs) and *Lactococcus lactis*.
3. To gain insight into the mechanisms involved in immune-mediated

beta-cell death aimed at harnessing the beta-cell against autoimmune attack.
4. To unravel the means of communication between beta-cells and the immune system in order to interfere with beta-cell destruction and propagation of the beta-cell destruction process.
5. To explore genetic variants responsible for the response to interventions allowing individualised therapies.
6. To build a consortium spanning basic and clinical research to allow new and individualised therapeutic approaches for clinical interventions in T1D in the future.

The Relation of NAIMIT with the European Commission

From the beginning, the EC assigned one scientific officer to NAIMIT. This person knew the project and the consortium well and was our liaison with the EC. An intense relationship grew with the coordinator, with direct email and phone contact to discuss any concerns of administration and finances. This relationship was crucial to the success of NAIMIT as questions were answered immediately and administrative burden was alleviated. Because, indeed, administrative burden exists, also in the coordination office, not only an administrative coordinator was appointed, but also a financial officer, with a financial office behind her. In addition, all partners had their financial officers also standing by and guiding the principal investigators in matters of financial reporting and auditing. The EC has very strict rules, which are sometimes surreal for researchers, so financial and administrative experts are essential as part of the team.

The Glue within NAIMIT

As stated, the NAIMIT consortium was a true consortium, but still, the nuclei of people who knew each other very well and saw each other frequently, came together with people who were a little less familiar with the others. Thus, communication strategies, with 'forced' communication were essential. In the first year, consortium phone conferences were organised every 3 months, with steering committee phone conferences every 6 months throughout the project. *Ad hoc* phone conferences were called when matters of scientific, but in particular financial or strategic, nature arose. Intense exchanges of techniques, of PhD students and postdocs were organised, peaking in the first 2 years, yielding lasting collaborations and joint publications, as well as additional grant opportunities for partners. The SMEs were heavily involved, hosting PhD students from partners in their facilities to learn techniques and share knowledge. Yearly, a scientific symposium of several days was organised at the site of one of the partners, where confidential data on the progress of the WPs were shared. This was crucial in order to allow progress of the work, but was only possible thanks to a balanced document stating the rules of the consortium (Consortium Agreement), thus creating peace of mind for researchers and in particular the SMEs on confidentiality and sharing of knowledge. In addition, our yearly meetings were also the occasion to bring in external advice from the Scientific Advisory Board. This board was essential in advising the partners and pointing to strengths, weaknesses, threats and most importantly opportunities for the consortium.

Not only is internal communication and communication with the EC important, but also, and perhaps even more importantly, NAIMIT showed its results to the taxpayers as NAIMIT could only exist thanks to community money. A whole communication strategy, with a website (www.naimit.eu) was established and NAIMIT partners spoke to press, lay and scientific, on many occasions. As such, NAIMIT participated in the Open Door Day of the EC in Brussels (May 2013) and NAIMIT was invited to present 'How to write and run a EC project successfully' at the occasion of the Infoday for the launch of Horizon 2020 (November 2013), the new funding scheme of the EC. On the website of NAIMIT, short presentations of the work within NAIMIT have been posted (global overview, SME presentation, partners, interim results, publications, etc.) NAIMIT further participates in national public initiatives in different countries. Regular contact is also kept with the JDRF, in lobbying together at the heart of the EC for attention for T1D research within Horizon 2020.

The Main Results of NAIMIT

Work Package 1 – Re-educating Antigen-presenting Cells

The work within WP 1 (WP1) was designed to interfere with antigen-specific autoimmunity, but with minimal impact on the global immune system. In this 'bench to clinical assessment' WP, autologous DCs are rendered tolerance-inducing in an antigen-specific manner. It was the aim to modulate DCs *ex vivo* towards a tolerogenic phenotype using 'natural' mediators (namely active VitD ($1,25(OH)_2D_3$) and/or GCs).[1] Tolerogenic DCs are being manipulated to orchestrate beta-cell-specific tolerance, by pulsing them with beta-cell auto-antigenic peptide epitopes, such as proinsulin C19-A3. Intense collaborations on comparing preclinical and clinical findings demonstrated the major difference between the nature of human and murine DC and their responses to VitD, as well as their characteristics needed for tolerogenicity. Data are now available on three models: non-obese diabetic (NOD) mice, rat insulin promoter-lymphocytic choriomeningitis virus glycoprotein (RIP-LCMV) mice and human leukocyte antigen-DR4 transgenic (HLA-DR4 Tg) mice (see WP2).[2] Besides this basic scientific work, most efforts were put on translating the knowledge to clinic, allowing as soon as possible the introduction of this interesting tool into patients.[3] For this, good manufacturing practices (GMP)-grade media and supplements have been introduced in the protocols, standard operating procedures (SOPs) validated, thus upgrading the tolerogenic DCs to a GMP cell product. Together with the data showing that tolerogenic DCs can be induced from monocytes of T1D patients, we are encouraged and on track to proceed with preparations of clinical-grade modulated DC-vaccine for the first-in-man study in the near future.

Work Package 2 – Restoring the T-cell Balance

This WP aims to restore the T-cell balance through an antigen-specific route that avoids global immune suppression. It builds upon the emerging programme of peptide immunotherapy (PIT), in which naturally processed and presented peptide fragments from major beta-cell auto-antigens are administered intradermally to promote the generation of islet-specific Tregs (IS-Tregs). Use of multiple peptides to enhance the power and breadth of the approach will be a major asset. Furthermore, topical adjuvants such as VitD, retinoic acid and GCs are being studied for their potential to enhance PIT. Building on NAIMIT, additional extra-mural funding (Wellcome Trust) has been obtained via a competitive award for the chemical and toxicological testing of the cocktail, as well as GMP-grade synthesis, through to preparation for a phase I study. Also a preclinical model has been established, in which HLA-DR4 Tg mice are rendered 'autoimmune' by immunisation with proinsulin and this model is being used for studying the peptide interventions (single and multipep) for prevention and intervention in diabetes. Finally, an extensive and operational clinical network of biological samples from new-onset cases of T1D is being established for preclinical and clinical intervention studies, in order to prepare eventual interventions and proof of concept in these patients.[4,5]

Table 1: Table Deliverable List

WP	Deliverable Name	Delivery Month	Reached
1.1	Generating reproducible, stable tolerogenic dendritic cells (DCs) by modulation with vitamin D, derivatives thereof, and/or GCs	24	√
1.2	Determination of mechanism of action of tolerogenic DCs	36	√
1.3	Upgrade to good manufacturing practices (GMP) cell product	48	√
1.4	Identification and validation of biomarkers of immune modulation in preclinical models	54	√
1.5	Definition of safety of clinical therapy with modulated DCs *in vivo* (phase I study)	60	
1.6	Identification of biomarkers of disease modulation	60	
2.1	Multi-peptide immunotherapy (PIT) – Evaluation of safety of multi-peptide immunotherapy using combinations of naturally processed and presented epitopes of islet autoantigens	36	√
2.2	Multi-PIT – Evaluation of how this therapeutic approach affects the balance of islet autoreactive pro-inflammatory and Tregs in type 1 diabetes mellitus (T1DM) patients	42	√
2.3	PIT with topical and systemic adjuvants – Evaluation of the effects of topical adjuvants on the tolerogenic environment in skin following saline injection	48	√
2.4	PIT with topical and systemic adjuvants – Evaluation of the effects of topical adjuvants on the balance of peripheral T cells specific for co-administered islet peptide	48	X
2.5	Identification of site of beta-cell-specific Treg development in preclinical models (thymus versus peripheral immune system; induced and natural Tregs)	42	√
2.6	GMP protocols for islet-specific interleukin-10 secreting regulatory T cells (ISIS-Treg) – Establishment of conditions to yield requisite number, purity and function of ISIS-Tregs	42	√
2.7	Phase I study of adoptive cellular therapy for T1DM – Evaluation of safety of adoptive transfer of ISIS-Tregs	60	
2.8	Phase I study of adoptive cellular therapy for T1DM – Evaluation of effect of adoptively transferred ISIS-Tregs on autoreactive T-cell balance	60	
3.1	Generation of beta-cell-specific antigen epitope/major histocompatibility complex (MHC) complexes via creation of T-cell clones from T1DM patients	12	√
3.2	Generation of a panel of soluble monoclonal T cell receptors (mTCRs) directed at beta-cell-specific antigen epitope/MHC complexes derived from TCRs from T-cell clones coming from T1DM patients	18	√
3.3	Generation of fluorescently labelled soluble mTCRs	24	√
3.4	Generation of fused soluble mTCRs to cytokines (interleukin [IL]-4 and IL-13)	30	√
3.5	Insight into influence of immune and metabolic stimuli on epitope presentation numbers on both human beta-cells and surrounding antigen-presenting cells (APCs)	36	X
3.6	Insight into the immunomodulatory effect of mTCRs *in vitro*	42	√
3.7	Insight into the immunomodulatory potential of mTCRs in preclinical models of T1DM	48	√
3.8	Selection of mTCRs of choice	48	X
3.9	GMP-grade mTCRs of choice	54	X
3.10	Toxicity profile in humans (phase I)	60	
3.11	Preliminary data on immunomodulatory effect in T1DM patients (phase I)	60	
4.1	Effect of probiotics on diabetes progression in preclinical models of T1DM	36	√
4.2	Characterisation of the way oral probiotics administration affects mucosal immunity in preclinical models of T1DM	36	√
4.3	Identification of gut and mucosal immunity biomarkers of disease progression or intervention	48	√
4.4	Generation of ActoBiotics™ secreting autoantigens (full insulin and peptides) alone, or along with tolerance-enhancing factors	12	√
4.5	Immune-modulating effects of ActoBiotics™ in preclinical models of T1DM	24	√
4.6	Effects of ActoBiotics™ in preclinical models of T1DM on diabetes arrest	42	√
4.7	GMP-grade ActoBiotics™	54	√
4.8	Proof of concept phase I study with probiotics for the induction of mucosal tolerance in T1DM	60	
4.9	Phase I study using ActoBiotics™ treatment in T1DM	60	
5.1	Identification of the genes and proteins involved in the 'dialogue' between stressed beta-cells and the immune system	48	√
5.2	Elucidation of how vitamin D and its derivatives modulate the mediators described	48	√
5.3	Effects of immune stress on beta-cell antigen presentation	42	√
5.4	Characterisation of the function of candidate genes for T1DM at the beta-cell level	60	
5.5	Identification of novel molecular targets to prevent immune stress-induced beta-cell destruction and amplification of the immune response	60	
5.6	Generation of silencing RNA (siRNA) and knock-out (KO) mice to intervene on targets promoting beta-cell protection and restoration	48	√
6.1	Identification of the genetic vitamin D system profiles that can be used for patient stratification in DC targeting interventions using vitamin D and its derivatives	18	√
6.2	Identification of the genetic vitamin D system profiles that can be used for patient stratification in T-lymphocyte targeting interventions using vitamin D and its derivatives	24	√
6.3	Identification of the genetic GC system profiles that can be used for patient stratification in DC targeting intervention using GCs	18	√
6.4	Identification of the genetic GC system profiles that can be used for patient stratification in T lymphocyte targeting intervention using GCs	36	√
6.5	Vitamin D action gene signatures in human monocytes and DCs	42	√
6.6	GC action gene signatures in human monocytes and DCs	48	X
6.7	Elucidation of CYP27B1 responsiveness to $1.25(OH)_2D_3$ in monocytes and DCs	54	√
6.8	Design of a pharmacogenetic decision tree in vitamin D and GC intervention	60	

Work Package 3 – T-cell Receptor-directed Immunotherapy

In this WP, the body's own system of recognising antigens on the surface of cells, namely the T-cell receptor (TCR), is being exploited by a very innovative technology, developed by the SME partner ImmunoCore.[6] Soluble mTCRs directed against specific beta-cell antigen epitopes in the context of the common human leukocyte antigen-A2 (HLA-A2) (A*0201) molecule, an allele present in the majority of T1D patients, or its mouse equivalent, have been engineered. These allow target-specific delivery of therapeutic agents. Different pathways have been taken: first linking mTCRs directed against beta-cell specific antigens specific for the mouse system have been linked to interleukin (IL)-4, IL-13 and IL-10 in order to perform proof of concept trials in preclinical mouse models (NOD). IL-10 constructs were too low in activity to merit *in vivo* testing in mouse models and have thus been discontinued and data on IL-4 and IL-13 were disappointing as treatment with these TCRs could not delay diabetes recurrence in NOD mice. Secondly, major mTCR engineering and intense collaborations between different NAIMIT beneficiaries have allowed the SME ImmunoCore to go indepth into the synthesis of human mTCRs directed against beta-cell autoantigens. It has become evident that all autoantigens identified until now, have very low binding affinity, thus making easy synthesis of mTCRs a challenge. However we have been successful in making mTCR specific for pre-proinsulin, overcoming significant technical barriers due to the low affinity of the wild type receptor. This was achieved in part as a result of targeting mutations to the regions of the TCR making direct contact with the target MHC-peptide, identified from a high-resolution crystal structure and additionally elongating other regions to bring them into contact with the MHC-peptide. Recently, pico-Molar affinity was achieved, with a binding half-life of over 14 hours, which is a significant achievement for a sub-optimal autoimmune TCR. Thus this tool is ready for linking to, for example, imaging molecules and will be explored for imaging of human beta-cells.

Work Package 4 – Mucosal Intervention for Tolerance Restoration

Here focus is put on induction of mucosa-mediated tolerance to islet antigens. Orally administered antigen encounters the gut-associated lymphoid tissue (GALT), a well-developed immune network that not only evolved to protect the host from ingested pathogens, but also developed the property of preventing the host from reacting to ingested proteins. Modulation of immune-responses in GALT has been shown to be relevant to prevent/delay autoimmune diabetes onset.[7] In particular we explored the therapeutic potential of an original tool introduced by SME ActoGeniX, in which recombinant *L. lactis* (ActoBiotics™) is a carrier for peptides, in association with immunomodulatory molecules, allowing delivery of antigen to the GALT. We demonstrated that introduction of beta-cell autoantigens, in particular proinsulin and glutamic acid decarboxylase (GAD), combined with IL-10 delivery and a short course of subtherapeutic doses of antiCD3 antibodies can reverse diabetes in newly diagnosed diabetic NOD mice in over 60 % of cases. This therapeutic effect is combined with the induction of CD4+CD25+FoxP3+ regulatory T cells. By using genetically manipulated models (FoxP3-DTR NOD mice), we could demonstrate that eliminating the FoxP3+ T cells, broke the tolerance installed by the ActoBiotics™ therapy.[8,9] Clinical grade strains of *L. lactis* (stably genomically integrated constructs instead of plasmid-driven) have been prepared by ActoGeniX and have been tested in NOD mice. Exactly the same protection as with the plasmid constructs is demonstrated. Finally, laser-capture microdissection of islets (endocrine portion and insulitis separately) allowed analysis of messenger RNA (mRNA) and micro RNA (miRNA) patterns. Preliminary data show major alterations in the gene expression in pancreases of mice treated with the ActoBiotics™ therapy. In the meantime, negotiations on the design of a clinical trial in humans with T1D are ongoing between ActoGeniX and different industrial partners as well as international regulators.

Work Package 5 – Beta-cell Protection and Restoration – Dialogue with the Immune System

In this distinctive WP, we focus on the role of the beta-cell in its own destruction and specifically on the way in which the immune system and the beta-cell communicate. We have obtained significant insights in the gene networks induced by IL-1β and tumour necrosis factor alpha (TNFα) as well as genes downstream of STAT-1 and IRF-1 using microarray and proteomic techniques in mouse and rat models for T1D and by RNA sequencing of human islets. A role for several candidate genes for T1D, in beta-cell responses to viral infections has been identified.[10–12] This was the first evidence that candidate genes for T1D may act at the beta-cell level, modulating both beta-cell apoptosis and the virus-induced dialogue between beta-cells and the immune system. New observations, obtained by RNA sequencing, indicate that >60 % of the known candidate genes for T1D are expressed in human islets and have detectable changes in expression following exposure to pro-inflammatory cytokines. Further, the impact of $1,25(OH)_2D_3$ on C57Bl6 mouse islets, exposed to inflammatory cytokines (Interleukin-1 beta [IL1β] and interferon-gamma [IFNν]), was studied by microarray analysis. A major impact was seen on chemokine and cytokine expression.[13] Finally, experiments in a rat model for T1D (LEW.1AR1-iddm) have been started and many new tools (miRNAs) have been designed allowing better analysis of the dialogue between the beta-cell and the immune system. New experiments, utilising pancreatic material from type 1 diabetic patients demonstrate that some markers of ER stress are up-regulated in islets from T1D patients, providing clinical support for our experimental approaches. Importantly, collaborative work inside NAIMIT, has identified a novel role for the Th17 cells and the cytokine IL-17 in the dialogue between beta-cells and the immune system, which contributes to trigger insulitis and beta-cell loss.[14,15]

Work Package 6 – Pharmacogenetics – Towards Individualised Therapies

This WP is built on the hypothesis that interventions should be individualised and tailored to the genetic footprint of the disease in any individual patient. The purpose was to link up with WP1 and WP2, to explore possible genetic signatures to predict responses of DCs and T-cells to VitD and GCs, depending on the presence of polymorphisms in crucial genes in the signal transduction and metabolism of these steroids. During the first year of NAIMIT, focus for this WP was concentrated on organising the logistic network between the partners involved in WP6 and in establishing SOPs on how to proceed with optimal sample collection, in order to provide samples to the 'genetics' partners of every patient and control donor where DC and T cells are being isolated. SOPs were established and major efforts on minimising blood volume were made. During the first years of NAIMIT, different batches of blood samples from healthy controls and T1D patients have been genotyped for HLA, VitD and GC polymorphisms. The results are at present being linked to functional DC and T-cell parameters. In the meantime, further characterisation of the VitD-related genes that are involved in DC and T cell behaviour are being studied with preliminary results for VitD pathway gene expression analysis of lymphocytes from healthy controls in relation to genotypes.[16] Now the first data on polymorphisms on genes involved in the VitD metabolism, transport

or action are emerging and to our greatest satisfaction patterns of associations are emerging. Of interest, the same polymorphisms are emerging both in DC and in T lymphocytes predicting effects of VitD, thus opening truly the possibility of personalised medicine and selection of those individuals who may benefit most or not at all from a treatment involving VitD.

Expected Final Results and Potential Impact

The predicted impact of the present project is considerable, both on a scientific and a therapeutic level. We have managed to execute this work with great energy, with all partners contributing to the goals of the project. The cell therapies, the antigen-based approaches, the exploitation of the natural immunomodulators and, of great interest, the introduction of the new tools for tolerance induction, all hold great promise. Research has progressed well in all WPs (see *Table 1*), with 32 out of 37 of the deliverables reached to date, and the first steps to the clinic are within reach. Many interactions have also taken place between our NAIMIT consortium and other FP7 consortia dealing with T1D. In the dissemination arena, the up-to-date internet page has attracted an important audience. Also, the number of scientific publications has increased from 11 in year one to 44 in year 4, with many collaborative publications.

In conclusion, NAIMIT was a project aimed at bringing together a consortium of scientists with the purpose of studying the interplay between the beta-cell and the immune system that lead to T1D, in order to better understand the disease and put forward therapeutic solutions. Our mission is not finished, we did not cure T1D, but many of our efforts are at the brink of being tested in humans. The partners of NAIMIT all have the feeling 'if only we could continue …', but unfortunately the FP7 programme is ending and alternative funding needs to be found. The positive point is that one of the first calls within the Innovative Medicines Initiative 2 (IMI2) initiative of the EU has 'T1D' as a target. However, IMI2 financing is quite different from FP7, as it is much more applied and industry driven, thus preventing the whole NAIMIT consortium to proceed into this initiative. Within Horizon 2020 we are eagerly awaiting for T1D to come onto the horizon. ■

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